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ORIGINAL ARTICLE

Endocrinal disturbances and systemic inflammation in chronic obstructive pulmonary disease (COPD)

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Abstract COPD is no longer considered to affect only the lungs and airways but also the rest of the body. The systemic manifestations of COPD include a number of endocrine disorders such as those involving the pituitary, thyroid, gonads, adrenals and pancreas.

The aim of this work is to detect the endocrinal and inflammatory changes in COPD patients during stability of the disease and the effect of acute exacerbation on these changes.

Subjects and methods: Twenty acute exacerbated COPD (AECOPD) male patients with acute respiratory failure (ARF) were included in this study as a patient group and a control group which included 10 healthy age-matched males with normal pulmonary functions and without any of the exclusion criteria. For patients enrolled in this study, measurement of serum levels of sex hormones [total testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH)], insulin like growth factor-1 (IGF-1) and C-reactive protein (CRP) were done on admission and 1 month after hospital discharge. For healthy group, the previous measurements were done once only.

Results: There were statistically significant decrease in serum testosterone and IGF-1 levels in patients after stabilization than those in the control group with more decrease of their levels during exacerbation and the difference between their levels in patients during exacerbation and after stabilization was statistically highly significant. As regards serum LH and FSH, there were statistically highly significant increase in their levels in COPD patients during exacerbation than those in the control group but there were non-significant differences in these hormones levels between the patients after stabilization and the control group. As regards serum CRP, there was highly significant increase in its serum level in patients in both exacerbation and after stabilization than that in the control group. The level of CRP in patients during exacerbation was higher than that after stabilization and the difference was statistically highly significant. As regards disease severity, there were statistically highly significant decrease in testosterone level in severe to very severe COPD patient group than that in mild

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to moderate one. There was also statistically significant decrease in serum IGF-1 level in severe to very severe COPD patient group than that in mild to moderate one. There was statistically highly significant increase in serum CRP level in severe to very severe COPD patient group than that in mild to moderate one. On the other hand, there was statistically non-significant increase in serum LH and FSH levels in severe to very severe COPD patient group than those in mild to moderate one. There were statistically highly significant positive correlations between serum testosterone levels and both FEV₁% predicted and PaO₂. There were also statistically highly significant positive correlations between serum IGF-1 levels and both FEV₁% predicted and PaO₂ and also between serum CRP levels and PaCO₂ in patients during exacerbation. Also during exacerbation, there was statistically highly significant negative correlation between serum CRP levels and FEV₁% predicted.

Conclusion: COPD leads to alterations in serum levels of sex hormones (testosterone, LH and FSH), IGF-1 and CRP. There was decrease in testosterone hormone levels of male stable COPD patients and this decrease was more evident, with compensatory increase in LH and FSH hormones levels, during exacerbation period when hypoxemia is more significant. CRP level is increased even in stable COPD and this rise is magnified with increased disease severity. IGF-1 decreased in stable COPD patients with more decrease in its level during acute exacerbation.

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Introduction

COPD is associated with low grade systemic inflammation that may be responsible for the systemic effects of the disease; malnutrition, muscle wasting, osteoporosis, cardiovascular disease, type II diabetes mellitus, anemia and depression [1].

COPD is no longer considered to affect only the lungs and airways but also the rest of the body. The systemic manifestations of COPD include a number of endocrine disorders such as those involving the pituitary, thyroid, gonads, adrenals and pancreas [3]. There are several studies examining the endocrine system of COPD patients, generally in stable cases [4].

Growth hormone provides stimulation of muscle growth and development. Growth hormone exerts its effects primarily by increasing levels of insulin-like growth factors (IGF). Increasing age, systemic corticosteroids commonly used to treat COPD exacerbations are known to down-regulate the growth hormone system [5]. The data that exist suggest that IGF-1 levels in stable COPD patients tend to be low consistent with the impression that the growth hormone axis is suppressed by chronic disease [6]. On the other hand, a few studies suggested increased growth hormone concentrations in COPD and especially in hypoxemic COPD [7].

Decreased anabolic hormone levels are commonly described in several chronic or critical illnesses including; chronic respiratory diseases [8]. Peripheral muscle wasting, osteoporosis, sexual dysfunction, immunological alterations, memory loss, diminished energy and vitality are among the clinical consequences of hypogonadal state [4,9]. The aim of this work is to detect the endocrinal and inflammatory changes in COPD patients during stability of the disease and the effect of acute exacerbation on these changes.

Subjects and methods

This study was conducted during the period from May 2009 to October 2010 at Chest and Clinical Pathology Departments, Zagazig University Hospitals.

Subjects included in this study comprised twenty acute exacerbated COPD (AECOPD) male patients with acute

respiratory failure (ARF) as a patient group and ten healthy age-matched males with normal pulmonary function and without any of the exclusion criteria as a control group.

The diagnosis of COPD and acute exacerbation of COPD was established according to GOLD criteria [10]. Patients with acute exacerbation of COPD admitted to respiratory intensive care unit (RICU) were enrolled in this study. Diagnostic criteria for ARF were respiratory acidosis (pH < 7.35, PaCO₂ > 45 mmHg) and PaO₂/FiO₂ < 200 and/or evidence of respiratory distress (respiratory rate ≥ 30/min, accessory respiratory muscle use, paradoxical breathing or intercostal muscle retraction) [11].

Spirometric classification of disease severity (mild, moderate, severe and very severe) was done according to GOLD criteria [10] after stabilization (1 month after hospital discharge).

Exclusion criteria

Patients who need mechanical ventilation or who use drugs may interfere with serum hormone levels, infections, malignancy, significant cardiac, renal, hepatic, metabolic or endocrine disturbances or neurological diseases were excluded [12].

All enrolled individuals were subjected to the following:

- (1) Thorough medical history stressing on smoking habit.
- (2) Full clinical examination.
- (3) Plain chest X-ray (postero-anterior and lateral views).
- (4) Routine laboratory investigations (CBC, liver and kidney functions).
- (5) Pulmonary function tests: were done on the first day of admission and 1 month after hospital discharge (after stabilization). Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured with Sensor Medicus 2450 computerized pulmonary function apparatus. One month after hospital discharge, patients with FEV₁ ≥ 80% of predicted value were considered mild, 50% ≤ FEV₁ < 80% of predicted value were considered moderate, 30% ≤ FEV₁ < 50% of predicted value were considered severe and FEV₁ < 30% of predicted value were considered very severe [10].

- (6) Arterial blood gas (ABG) analysis: was done on the first day of admission and 1 month after hospital discharge (after stabilization). It was done to check arterial oxygen tension (PaO₂), arterial carbon dioxide tension (PaCO₂) and arterial pH using blood gas analyzer (ABL-330- Radiometer Copenhagen).
- (7) Serum CRP estimation: [13]

BN ProSpec was used in CRP estimation. Polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein sample. The result is evaluated by comparison with a standard of known concentration (CARDIOPHASE DADE BEHRING, Newark, USA).

- (8) Serum IGF-1 measurement: [14]

IGF-1 was determined using ELISA kit from BioSource, Belgium. The technique includes an extraction step in which IGF-1 is separated from its binding protein by ethanol-HCl acid extraction solution. The technique uses antibodies with high affinity and specificity for two different epitopes on IGF-1. A first monoclonal anti-IGF-1 antibody bound to a polystyrene well will capture the IGF-1 of the sample in the presence of a second alkaline phosphatase conjugated monoclonal anti-IGF-1 antibody. Following incubation and washing, the chromogen/substrate was added and intensity of color was measured at 405 nm.

- (9) Serum total testosterone, LH and FSH assay: [15].

They were measured using electro-chemiluminescence immunoassay on Cobase 411. The assay employs two monoclonal antibodies both specifically directed against the parameters measured one is biotinylated (interact with streptavidin-coated microparticles) and the other labeled with ruthenium (responsible for chemiluminescence emission).

For the healthy group, the previous measurements were done once only.

All patients were followed until hospital discharge and 1 month later.

For patients, blood samples were collected at the first day of RICU admission and 1 month after hospital discharge with stoppage of steroid therapy (if it is continued after hospital discharge) at least 5 days before hormonal measurement. After centrifugation, sera were kept frozen at -80 °C until assayed [11].

Statistical analysis

Statistical analysis was performed with the SPSS statistical software package (SPSS Inc., Chicago, IL).

Data presented by mean \pm SD for quantitative continuous data was calculated by one way analysis for variance (*F* test).

Comparing mean values of paired data of patients during exacerbation and after stabilization were done by paired (*t*) test, also comparison of mean values of patients data whether during exacerbation or after stabilization with controls were done by independent (*t*) test.

Correlation coefficient (*r*) were calculated for testing association between quantitative variables. *P*-value < 0.05 is considered significant.

Results

Table 1 showed demographic data of the studied subjects at time of admission. There were statistically non-significant differences regarding age, BMI and pack-year of smoking between patients and control groups.

Table 2 showed statistically highly significant differences regarding FEV₁% predicted (*P* = 0.006), PaO₂ (*P* = 0.001) and PaCO₂ (*P* = 0.001) when these parameters were compared in patients during exacerbation (at time of admission) and after stabilization (1 month after hospital discharge).

Table 3 showed statistically highly significant differences (*P* = 0.001) in patients during exacerbation and after

Table 1 Demographic characteristics of the studied subjects at time of admission.

Parameter	Patients group (<i>n</i> = 20)	Control group (<i>n</i> = 10)	P-value
Age (years)	57.34 \pm 12.65	55.58 \pm 13.21	0.8
BMI (kg/m ²)	23.61 \pm 4.86	25.32 \pm 5.72	0.39
Smoking (pack-year)	48.57 \pm 15.37	46.39 \pm 13.46	0.71

Table 2 Pulmonary function tests and arterial blood gas analysis of patients on admission (during exacerbation) and 1 month after hospital discharge (after stabilization) and controls.

Parameter	During exacerbation patients (<i>n</i> = 20)	After stabilization (<i>n</i> = 20)	Controls (<i>n</i> = 10)	P-value*
FEV ₁ % predicted	46.39 \pm 12.15	54.63 \pm 13.29	91.23 \pm 14.46	0.006
FVC% predicted	50.8 \pm 13.14	85.21 \pm 25.32	94.05 \pm 15.38	0.001
FEV ₁ /FVC	48.3 \pm 13.96	59.87 \pm 15.28	80.4 \pm 9.53	0.006
pH	7.31 \pm 0.06	7.42 \pm 0.08	7.37 \pm 0.14	0.01
PaO ₂ (mmHg)	46.21 \pm 11.32	80.24 \pm 20.47	94.54 \pm 5.93	0.001
PaCO ₂ (mmHg)	75.23 \pm 16.49	42.83 \pm 11.73	37.34 \pm 3.51	0.001

* P-value is obtained by comparison of patients during exacerbation (on admission) and after stabilization (1 month after hospital discharge).

Table 3 Serum sex hormones, IGF-1 and CRP levels on admission (during exacerbation) and 1 month after hospital discharge (after stabilization) in patient group in comparison to controls.

Parameter	During exacerbation (n = 20)	After stabilization (n = 20)	Controls (n = 10)	<i>P</i> -value *	<i>P</i> -value **	<i>P</i> -value ***
Serum testosterone (ng/ml)	1.4 ± 0.03	2.5 ± 0.71	5.7 ± 1.72	0.001	0.02	0.03
Serum LH (mIU/ml)	14.26 ± 3.21	6.31 ± 2.01	5.03 ± 1.53	0.001	0.0001	0.09
Serum FSH (mIU/ml)	14.03 ± 3.01	6.98 ± 2.23	5.63 ± 1.62	0.001	0.0001	0.14
Serum IGF-1 (ng/ml)	56.23 ± 17.4	93.61 ± 18.8	135.21 ± 24.4	0.001	0.0001	0.0001
Serum CRP (mg/dl)	43.7 ± 5.09	7.35 ± 1.1	0.3 ± 0.01	0.001	0.0001	0.0001

* *P*-value is obtained by the comparison of patients during exacerbation and after stabilization.

** *P*-value is obtained by the comparison of patients during exacerbation and controls.

*** *P*-value is obtained by the comparison of patients after stabilization and controls.

stabilization as regards serum sex hormones, IGF-1 and CRP levels. There was statistically significant decrease in serum testosterone level in patients during exacerbation ($P = 0.02$) and also after stabilization ($P = 0.03$) than that in the control group. Statistically highly significant decrease in serum IGF-1 level ($P = 0.0001$) in patients during exacerbation and after stabilization than that in control group was observed. As regards serum LH and FSH, there were statistically highly significant increase in their levels in COPD patients during exacerbation than that in the control group ($P = 0.0001$) but there were non-significant differences ($P = 0.09$) and ($P = 0.14$) in these hormones levels respectively between the patients after stabilization and the control group. As regards serum CRP, there was highly significant increase in its serum level in patients both during exacerbation and after stabilization than that in control group ($P = 0.0001$).

Table 4 showed statistically highly significant decrease in testosterone level ($P = 0.0001$) in severe to very severe COPD patient group than that in mild to moderate one. There was also statistically significant decrease in serum IGF-1 level in severe to very severe COPD patient group than that in mild to moderate one ($P = 0.01$). There was highly significant increase in serum CRP level in severe to very severe COPD patient group than that in mild to moderate one ($P = 0.0001$) but

the difference was statistically non-significant as regards serum LH and FSH levels ($P = 0.67$) and ($P = 0.69$) respectively between both groups.

Table 5 showed statistically highly significant positive correlations between serum testosterone levels and both FEV₁% predicted and PaO₂, serum IGF-1 levels and both FEV₁% predicted and PaO₂ and also between serum CRP levels and PaCO₂ in patients during exacerbation. Also, there was statistically highly significant negative correlation between serum CRP levels and FEV₁% predicted and this negative correlation was significant between serum CRP levels and PaO₂ and between serum testosterone levels and PaCO₂ in patients during exacerbation.

Table 6 showed statistically significant positive correlation between serum testosterone levels and FEV₁% predicted. But, there were statistically significant negative correlations between serum CRP levels and both FEV₁% predicted and PaO₂.

Discussion

Decreased anabolic hormone levels are commonly described in several chronic or clinical illnesses including; chronic

Table 4 Sex hormones, IGF-1 and CRP levels in patients group during stabilization regarding to disease severity.

Parameter	Mild to moderate COPD (n = 9)	Severe to very severe COPD (n = 11)	<i>P</i> -value
Serum testosterone (ng/ml)	2.7 ± 0.6	1.4 ± 0.4	0.0001
Serum LH (mIU/ml)	6.53 ± 2.12	7.02 ± 2.85	0.67
Serum FSH (mIU/ml)	6.63 ± 2.11	7.01 ± 2.12	0.69
Serum IGF-1 (ng/ml)	99.4 ± 17	75.8 ± 19	0.01
Serum CRP (mg/dl)	2.6 ± 0.61	8.6 ± 1.41	0.0001

Table 5 Correlation coefficient between each of serum sex hormones, IGF-1 and CRP levels and FEV₁% predicted, PaO₂ (mmHg) and PaCO₂ (mmHg) during exacerbation.

	Serum testosterone	Serum LH	Serum FSH	Serum IGF-1	Serum CRP
FEV ₁ % predicted	0.58**	-0.23	-0.28	0.74**	-0.71**
PaO ₂ (mmHg)	0.71**	-0.32	-0.33	0.70**	-0.51*
PaCO ₂ (mmHg)	-0.46*	0.28	0.22	-0.21	0.59**

* $P < 0.05$.

** $P < 0.01$.

Table 6 Correlation coefficient between each of serum sex hormones, IGF-1 and CRP levels and FEV₁% predicted, PaO₂ (mmHg) and PaCO₂ (mmHg) after stabilization.

	Serum testosterone	Serum LH	Serum FSH	Serum IGF-1	Serum CRP
FEV ₁ % predicted	0.53*	−0.43	−0.26	0.41	−0.49*
PaO ₂ (mmHg)	0.22	−0.14	−0.36	0.39	−0.45*
PaCO ₂ (mmHg)	−0.28	0.06	0.29	−0.35	0.16

* $P < 0.05$.

respiratory diseases [8]. Accumulating data indicate that anabolic hormone levels are low in COPD, although the underlying mechanisms are unclear [16]. In COPD, little is known about circulating IGF-1 concentrations. Some authors found a decrease in IGF-1, others found an increase [6]. The present study was performed to detect the endocrinal and inflammatory changes in COPD patients during stability of the disease and the effect of acute exacerbation on these changes.

We found statistically highly significant differences ($P = 0.001$) between patients during exacerbation and after stabilization as regards serum sex hormones, IGF-1 and CRP levels. Also, the differences were statistically highly significant ($P = 0.0001$) as regards serum LH, FSH, IGF-1 and CRP levels between patients during exacerbation and controls and also between patients after stabilization and controls regarding serum IGF-1 and CRP levels only (Table 3). Also, in our study, regarding disease severity, there was statistically highly significant decrease in testosterone level ($P = 0.0001$) in severe to very severe COPD patient group than that in mild to moderate one but the difference was statistically non-significant as regards serum LH and FSH levels ($P = 0.67$) and ($P = 0.69$) respectively between both groups. Regarding sex hormones, normally when testosterone level is decreased, a negative feedback of sex hormones on the hypothalamic-pituitary axis is lost and secretion of gonadotrophins (LH and FSH) increases [17].

Our results of sex hormones may be due to several mechanisms including; hypoxemia [18], obesity, glucocorticoid therapy, atrophy of leydig cells and increased cytokine concentrations [19,20].

Systemic inflammation has been suggested as a possible cause of low circulating testosterone concentrations in male patients with COPD [16] and this explains the statistically significant decrease of serum testosterone levels in COPD patients after stabilization than those in controls (Table 3).

Interestingly, there is a regulating loop between proinflammatory cytokines and anabolic steroids. Increased levels of proinflammatory cytokines as in acute exacerbation of COPD reduce testosterone secretion by interfering with leydig cell function [21].

Hypotestosteronemia in our study was accompanied with statistically highly significant increase in serum LH and FSH levels in patients during exacerbation than those in patients after stabilization and those in the control group (Table 3) and this testicular dysfunction is called hyper-gonadotrophic hypogonadism [11]. It depicts an increased compensatory gonadotrophins secretion from the hypothalamic-pituitary axis in order to correct the low circulating testosterone level [17].

In fact, a decrease in circulating testosterone concentrations and a compensatory increase in the circulating gonadotrophins

have been reported in healthy elderly men [22] and in patients with COPD [4].

Our results are in consistence with Akbas et al. [11] who reported reduced testosterone levels in COPD patients and suggested that hypogonadism may be due to a primary testicular atrophy in COPD.

One of the suggested underlying factors for hypogonadism is hypoxemia, which is present in a proportion of COPD patients [12]. Gosney [19] found smaller testis volume and leydig-cell atrophy in necropsy of COPD patients and suggested that this atrophy may be a consequence of hypoxic inhibition of pituitary synthesis or release of LH. Semple et al. [23] suggested that hypoxemia produces abnormalities of hypothalamic-pituitary-testicular function, rather than primary testicular dysfunction and they concluded that these hypoxemia-induced changes were reversible as testosterone concentration increased significantly in men recovering from a severe exacerbation of COPD. The findings of Aasebo et al. [24] supported these data as they showed that long-term oxygen treatment increased sexual function and testosterone levels.

Also, supporting to these data, serum testosterone was measured low in men exposed to high-altitude hypoxia [19], in patients with hypoxemic idiopathic pulmonary fibrosis and hospitalized hypoxemic COPD patients [18].

Another possible cause of the observed hypogonadism may be glucocorticoid-induced suppression of the adrenals, a direct inhibitory effect via testicular glucocorticoid receptors or decreased testosterone biosynthesis via reduced content of LH receptors in leydig cells [25].

Karadag et al. [12] study is in consistence with our results as they found significant differences in sex hormone levels during stable and exacerbation phases of COPD.

The decrease in androgens and compensatory increase in gonadotrophins during exacerbation phase when hypoxemia is more significant and subsequent regression of these alterations when disease is stabilized may be accepted as a compensatory reaction of hypothalamo-pituitary-gonadal axis against suppression of testicular function in COPD [12]. This may explain our results.

In this study, after stabilization of the disease, sex hormones levels returned back but didn't reach to normal levels as in controls. These results may be explained by the presence of low-grade systemic inflammation in stable COPD patients and there are high levels of proinflammatory cytokines as IL-6, TNF- α and CRP in stable COPD and these cytokines cause sex hormones alteration [11].

With disease improvement, suppressed hormones (testosterone) rebound as synthesis and secretion of them increase [23,26]. The normalization of hormones may take a long time. Elevation of testosterone to normal values was reported to

take 2–12 months [27]. A return of LH and FSH to normal ranges can take as long as the rise in testosterone [28].

In contrary, Svartberg et al. [29] reported that men having chronic bronchitis or emphysema didn't have reduction in testosterone levels, thus they speculate that it is not the disease per se that affects the hormone levels but the actual level of pulmonary function. Also, they hypothesize that the gradual decline in FEV₁% predicted is followed by a decline in testosterone and this may explain the decrease in serum testosterone levels with increasing severity of COPD. Our work is in agreement with Makarevich [30] who concluded that the intensity of sex hormone changes were correlated with the stage of COPD. As the severity of the disease increased, testosterone decreased and LH, FSH increased compensatively and they suggested that anabolic hormonal deficiency is a surrogate of disease severity especially in men.

In disagreement with our results, Laghi et al. [4] noticed in their study, that the severity of lung disease didn't predict the hormonal abnormalities, making chronic disease an unlikely cause of hypogonadism.

In the lung, CRP has protective functions in innate immune responses against bacteria and apoptotic cells. CRP enters the lung from plasma and is primarily produced by hepatocytes in response to IL-6 stimulation. Activated epithelial cells and increased numbers of alveolar macrophages and other inflammatory cells in COPD may release IL-6 into the circulation. This stimulates an acute-phase response and increases the level of plasma CRP [31].

Regarding serum CRP results in this study, the statistically highly significant increase of serum CRP levels in patients during exacerbation than those after stabilization is due to the fact that CRP levels rise rapidly during infection or after injury to just decline after the initial stimulus has vanished [32]. Also, we found that after stabilization of the disease, serum CRP levels were still higher in stable COPD patients than those in controls. These results may be explained by that the focus of systemic inflammation in COPD patients is still unclear. Several theories were previously suggested, including; local pulmonary inflammation due to actual or previous smoking, oxidative stress and tissue hypoxia known to increase cytokine levels [33]. Gan et al. [34] reported that individuals with chronic airflow limitation had significantly raised levels of CRP, fibrinogen, leucocytes and TNF- α indicating that persistent systemic inflammation is present in COPD. Even among non-current smokers, there was evidence for low-grade systemic inflammation in those with chronic airflow limitation. This suggests that, once COPD develops, cessation of smoking may not fully attenuate the inflammatory process associated with this condition. Increased serum CRP in stable COPD seems to be reduced by treatment with an inhaled corticosteroids [35].

Our result is in agreement with Pinto-Plata et al. [36]. They reported that the stable COPD patients had higher levels of inflammatory markers like CRP rather than smoker and non-smoker control groups.

Of all the investigated inflammatory markers in Piehl-Aulin et al. [37] study, serum CRP levels were significantly increased even in mild COPD (GOLD stage I) and remained significantly increased at the moderate and severe COPD stages and our results match this study.

The evidence for the presence of systemic inflammatory process was manifested in otherwise clinically stable patients

by an early and sustained rise of serum CRP with ascending disease severity [37].

Many previous studies are in agreement with our results of CRP and severity of COPD. de Torres et al. [38] reported that serum CRP level was significantly increased by aggravation of COPD reflecting the systemic inflammatory process in patients with severe disease. Also, they demonstrated that high CRP levels in COPD patients are due to the greater degree of airway obstruction and disease severity and CRP levels of patients who died tended to be higher than those who survived.

IGF-1 has been implicated in several important functions such as cell differentiation, growth and maintenance of skeletal muscle [39].

In our study, the highly significant decrease in IGF-1 levels in patients during acute exacerbation than those after stabilization and also in stable COPD patients than those in controls may be due to the fact that the bioavailability and the effects of IGF-1 are influenced by IGF-1 binding protein (IGFBP). Therefore, an increase in circulating levels of these proteins may decrease the levels of free IGF-1 [39]. Cytokines increase IGFBP-1 and IGFBP-4 and this results in a decreased free IGF-1 fraction. IL-6 performs its suppressive activity on IGF-1 via increased production of its binding protein [40].

Growth hormone (GH) mediates its major metabolic effects predominantly through IGF-1. The GH axis is suppressed in chronic diseases and this may partly explain the low IGF-1 levels and, also may explain that after stabilization of the COPD patients, IGF-1 levels increases but still remained lower than levels in healthy controls [41].

Our results are in consistence with Coskun et al. [42] and Kythreotis et al. [41]. They reported lower levels of serum IGF-1 in stable COPD patients than in healthy subjects and these levels tend to be lower in patients with COPD exacerbation.

In contrary, Debigare et al. [43] demonstrated an increase in circulating GH and IGF-1 in COPD patients. The increase in GH might reflect a non-specific response of the body to stress (hypoxemia) [42].

As the disease severity increases, the local inflammation is more pronounced and the proinflammatory cytokines increases, so the more the decrease of serum IGF-1 levels which is due to increase of IGFBP [44]. This may explain the significant decrease of serum IGF-1 level in severe to very severe COPD patient group than that in mild to moderate one. In consistence, Coskun et al. [42] found that IGF-1 levels were significantly decreased in very severe COPD patients compared to mild to moderate COPD patients.

Some authors advocate that low levels of IGF-1 might be increasing the severity of the disease particularly in COPD patients by adversely affecting the respiratory muscle [43].

Regarding correlation coefficient during exacerbation, there were statistically highly significant positive correlations between each of serum testosterone and IGF-1 levels and both FEV₁% predicted and PaO₂ and between serum CRP levels and PaCO₂ ($P < 0.01$). Also, there were statistically significant negative correlation between serum testosterone levels and PaCO₂ and between serum CRP levels and PaO₂ ($P < 0.05$) (Table 5).

Regarding correlation coefficient after stabilization of the disease, there were statistically significant positive correlation between serum testosterone levels and FEV₁% predicted and statistically significant negative correlations between serum

IGF-1 levels and PaCO₂ and between serum CRP levels and both FEV₁% predicted and PaO₂ ($P < 0.05$) (Table 6).

As regards serum testosterone correlations, our results are in agreement with Svartberg et al. [29] who concluded that both total and free testosterone were positively and independently associated with FVC% predicted and men with severe pulmonary obstruction (FEV₁ < 50% predicted in combination with FEV₁/FVC < 70%) had lower testosterone levels compared with the remaining study cohort.

Makarevich [30] assessed relation of sex hormone status and the stage of COPD. They concluded that the intensity of sex hormone changes were correlated with the stage of COPD.

Semple et al. [18] found low testosterone levels in acutely ill, hospitalized COPD patients with hypoxemia and reported that the degree of testosterone suppression was correlated to severity of arterial hypoxemia and hypercapnia and these results match our study results. Also, Karadag et al. [12] reported that, in COPD exacerbation, testosterone was positively correlated to PaO₂. In follow-up measurements, testosterone increased and LH decreased in parallel with the improvement in arterial blood gases.

In contrary, Debigare et al. [43] and Laghi et al. [4] didn't demonstrate an association between testosterone concentrations and PaO₂. The lack of association is due to serum testosterone levels tend not to fall to the hypogonadal range until PaO₂ drops below 55 mmHg [18], a threshold crossed by only 3 of their patients while breathing room air.

CRP (an inflammatory marker) has generated in the COPD field. CRP is an acute-phase reactant that increases in a very sensitive but non-specific way in most forms of tissue damage, inflammation and infection, all are very dynamic processes in patients with COPD [2].

As regards serum CRP correlations, our results in consistence with Gan et al. [45] who reported that elevated CRP is associated with decline in lung function and worsening of chronic COPD. Also, Rasmussen et al. [46] concluded that there is an association between inflammation in COPD and FEV₁ and FVC decline.

Our results also, agreed the results of de Torres et al. [38] study who reported that in stable COPD patients, CRP levels correlated mainly with physiological parameters, such as FEV₁, FVC and PaO₂ and explained the inverse correlation between CRP levels and PaO₂ as hypoxemia triggers oxidative stress and inflammation in COPD patients.

In contrary, Pinto-Plata et al. [36] demonstrated that there was no association between selected pulmonary function test measurements (FEV₁, TLCO) and CRP levels in COPD patients.

Regarding serum IGF-1 correlations, our results are in agreement with Spruit et al. [47] who reported that lower levels of serum IGF-1 were correlated with lower levels of FEV₁ in COPD patients and this result may be supported by that IGF-1 levels tend to be low in patients with COPD, which might be consistent with the impression that the growth hormone (GH) axis is suppressed by severe chronic disease [6].

Also, as regards PaO₂, many studies are in consistence with our work. Ursavas et al. [48] reported that the positive correlation between the decrease in IGF-1 levels and the decrease of PaO₂ may be due to several mechanisms as; acute hypoxemia decreases the rate of IGF-1 synthesis, the clearance rate of IGF-1 may have increased, acute hypoxemia significantly increased plasma concentration of IGFBP-1 which decreases

the free IGF-1 fraction and also chronic hypoxemia could have a direct effect on transcription of IGF-mRNA, similar to its effect on transcription of other proteins [49].

Conclusion

COPD leads to alterations in serum levels of sex hormones, IGF-1 and CRP. There was decrease in testosterone hormone levels of male stable COPD patients and this decrease was more evident, with compensatory increase in LH and FSH hormones levels, during exacerbation period when hypoxemia is more significant. CRP level is increased even in stable COPD and this rise is magnified with increased disease severity. IGF-1 decreased in stable COPD patients with more decrease in its level during acute exacerbation.

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